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Growth versus immunity – a redirection of the cell cycle?

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Diseases caused by plant pathogens significantly reduce growth and yield in agricultural crop production. Raising immunity in crops is therefore a major aim in breeding programs. However, efforts to enhance immunity are challenged by the occurrence of growth inhibition triggered by immunity that can be as detrimental as diseases. In this review, we will propose molecular models to explain the inhibitory growth-immunity crosstalk. We will briefly discuss why the resource reallocation model might not represent the driving force for the observed growth-immunity trade-offs. We suggest a model in which immunity redirects and initiates hormone signalling activities that can impair plant growth by antagonising cell cycle regulation and meristem activities.

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Introduction

Under current climates, biotic stress is a major threat in crop production accounting for up to 20–40% annual crop yield reduction [1]. In addition to more elaborated agricultural crop management and phytomedicine strategies, we need to generate crop cultivars with a higher yield under biotic stress. Plants have evolved a highly effective multi-layered immune system to encounter pathogen attack. Immunity relies on the recognition of non-self molecules of microbial origin that are defined as microbe-associated molecular patterns (MAMPs) and include fungal chitin, bacterial peptidoglycans, flagellin (flg) or elongation factor Tu (EF-Tu). MAMPs are recognised by plasma membrane-localised pattern recognition receptors (PRRs) thereby activating a broad repertoire of immune responses known as pattern-triggered immunity (PTI) to

stop invaders [2,3]. In response to PTI, pathogens have evolved counter defence strategies that are based on secreted effector proteins, whose action in the plant apoplast and cytosol enables the suppression of PTI and release of nutrients [4,5]. The detection of effector action by plant resistance (R) proteins that belong to the class of nucleotide-binding site leucine-rich repeat proteins (NLRs) activates effector-triggered immunity (ETI), which is characterised by higher immune response kinetics than PTI and involves cell death [6–8].

Based on this concept and assuming a sufficiently high selection pressure, one would expect that plants accumulate a highly diverse receptor arsenal to launch innate immune strategies that are almost unsurmountable by pathogens. In clear contrast, plants display a high variability in the degree of immunity [9] suggesting the existence of a downside of immunity. In fact, immunity is associated with fitness costs, and a hyper-active immune system can deplete any benefits in the absence of pathogens [10,11]. These fitness costs that range from growth inhibition to lethality are observed at the level of PTI and ETI [9,12,13] and can affect plant growth and yield to an extent equivalent to that caused by diseases [14–16]. Therefore, breeding for enhanced immunity and growth in crops must be balanced especially as we know that growth signalling suppresses immunity [17^{••},18^{••}]. This review will summarise our current understanding of growth-immunity trade-offs and propose a molecular basis of immunity-triggered growth inhibition. Focussing on roots, we discuss the function of hormones in the regulation of the cell cycle as driving force of growth, and highlight recent findings on the interplay of cell cycle and immunity.

The growth-immunity trade-offs

Studies on roots have greatly advanced our knowledge of growth processes. Root growth is based on the concerted activation of multiple signalling pathways that regulate cell proliferation at the stem cell niche as well as cell division and expansion via the cell cycle at the meristematic and elongation/differentiation zones, respectively [19–21]. Growth inhibition in response to immune activation [12,22,23] can significantly reduce grain yield as any disturbance of the vegetative-to-reproductive phase transition delays the initiation of reproductive processes [24]. This delay results in reduced seed number and filling [25]. That this is of significance beyond defined laboratory conditions was shown in field studies. For example, PTI activation in barley by naturally occurring adapted and non-adapted microbes of the phyllosphere

causes ~10% yield reduction [15]. The negative potential of the growth-immunity trade-off is obvious from genetic studies. In *Arabidopsis*, constitutive immunity (non-lethal autoimmunity) reduced growth and yield by up to 90% [9,16]. Moreover, natural populations of *Arabidopsis* carry genetically incompatible alleles of the PTI-regulator ACCELERATED CELL DEATH 6 (ACD6) whose combination results in F1 progenies with strong growth inhibition due to autoimmunity [9,26**].

Is immunity-triggered growth inhibition a default response?

Considering the high energy demand of immunity and growth, the observed growth-immunity trade-off might reflect a competition for available energy resources and nutrients that are too limited to be allocated to both processes simultaneously [10,11,15]. For instance, immunity can affect wheat growth under N depletion [11]. But under standard nutrient regimes, energy and nutrient availability appears not to be a limiting factor in crops [27] and a recent study did not observe a correlation between N or C limitation and defence [28]. In addition, PTI activation does not necessarily suppress growth. Treatment with the MAMP chitin blocks pathogen invasion by activating immune responses highly similar to flg or EF-Tu without affecting growth [29,30]. Moreover, the *Arabidopsis* ecotype C24 has elevated pathogen resistance due to immunity levels that are higher than that observed in the autoimmunity and dwarf mutant *cpr6-1*. However, C24 was not impaired in yield [16,31]. These studies indicate that PTI activation does not necessarily affect growth and this might hold true for ETI as well. Although resistance conferred by the NLR RPM1 affects growth and yield [14], overexpression of other R proteins does not seem to be costly to the plant [10]. Taken together, the growth-immunity trade-off is most likely not attributable to resource reallocation. Instead it appears as if the growth-immunity crosstalk is the result of a conflictive activation of pathways or sharing of signalling components by immune and growth signalling.

Hormones — mediators of growth and immune signalling

Hormones translate internal and external stimuli within and across cells thereby providing plants with a considerable degree of plasticity to grow and survive under changing environments. This complexity requires a tight regulation as individual hormone signalling pathways are intertwined and any regulatory disorder would impair this network and thus disturb growth or immunity. Various studies of the last decade have revised our understanding of the function of hormones in growth and immunity. The canonical growth hormones auxin, brassinosteroids (BR), gibberellins (GA), cytokinins (CY) and strigolactones (SL) were found to affect immune signalling, while the typical stress hormones salicylic acid (SA), jasmonates (JA), ethylene (ET) and abscisic acid (ABA) influence

growth and development [32–34]. These studies suggest that individual hormones mediate the mutually inhibitory growth-immunity crosstalk. The transition from a growth (non-stressed) to an active immunity modus and vice versa requires a hormone-orchestrated rewiring of growth and immune signalling. The contribution of hormones in growth-immunity trade-offs has recently been reviewed [35,36]. Here, we briefly summarise examples of specific hormones that provide a direct link to particular aspects of growth regulation. Recent studies highlighted the function of the BR pathway in suppressing PTI. Upon BR recognition, BRASSINOSTEROID-INSENSITIVE 1 (BRI1) together with BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1) initiates a signalling cascade in which the successive phosphorylation of BOTRYTIS-INDUCED KINASE 1 (BIK1), BRASSINOSTEROID-SIGNALLING KINASE 1 (BSK1) and BRI1-SUPPRESSOR 1 (BSU1) results in the inactivation of the negative regulator BRASSINOSTEROID-INSENSITIVE 2 (BIN2) and hence the activation of transcription factors (TFs) including bHLH HOMOLOG OF BR ENHANCED EXPRESSION2 INTERACTING WITH INCREASED LEAF INCLINATION1 BINDING bHLH1 (HBI1) and BRASSINAZOLE-RESISTANT1 (BZR1) [17**,37,38]. BR and especially the flg-induced PTI pathways share BAK1, BIK1 and BSK1 [37,39,40]. It is still not entirely clear how these proteins can serve BR and PTI pathways at the same time and if they participate in the growth-immunity crosstalk. Currently, the TFs BZR1 and HBI1 are considered crucial regulatory nodes in this crosstalk. Both can transcriptionally activate growth-related genes but negatively regulate immune responses and thus suppress PTI [17**,18**]. These studies indicate a prominent role of BR in growth-triggered suppression of PTI. But we are only just beginning to understand how PTI inhibits growth. The BR-PTI crosstalk depends on GA signalling since inhibition of GA synthesis abolishes the immunosuppressive BR effect. GA and BR co-treatment had an additive effect on blocking flg-triggered growth inhibition [18**]. In the absence of GA, DELLA proteins can interact with and inhibit the TFs PHYTOCHROME INTERACTING FACTORS (PIFs) and BZR1 and block growth responses. In the presence of GA, DELLA proteins are degraded and release PIFs and BZR1 to promote growth [41] and suppress PTI (see above). This is in accordance with results that showed that flg-mediated stabilisation of DELLA proteins contributed to PTI-triggered growth inhibition [42]. In addition to GA, auxin affects PTI. Navarro *et al.* [43] showed that PTI induced miR393 to silence the auxin receptors TIR1, AFB2 and AFB3 and enhanced resistance against the bacterial pathogen *Pseudomonas syringae*. Although this study provided a clear connection between PTI and the growth hormone auxin, it was not shown whether auxin receptor silencing correlated with growth inhibition. That impaired auxin signalling can contribute to the growth-immunity trade-off might be indicated by the dwarfed phenotype of non-lethal

autoimmunity mutants (e.g. *cpr5*, *cpr6* and *snc1*). This dwarfism was explained by elevated SA contents, which might stabilise AUX/IAA repressors and suppressed auxin-regulated genes [44]. JA might represent another hub in the growth-immunity crosstalk. JA treatment suppressed growth and was shown to inhibit auxin distribution in roots [45]. Moreover, JA ZIM DOMAIN (JAZ) proteins, which are suppressors of JA signalling, bind to DELLAs and disable their repressive interaction with growth promoting TFs. JA treatment, in turn, induces JAZ degradation thereby releasing the growth inhibitory activity of DELLAs [46,47,48**].

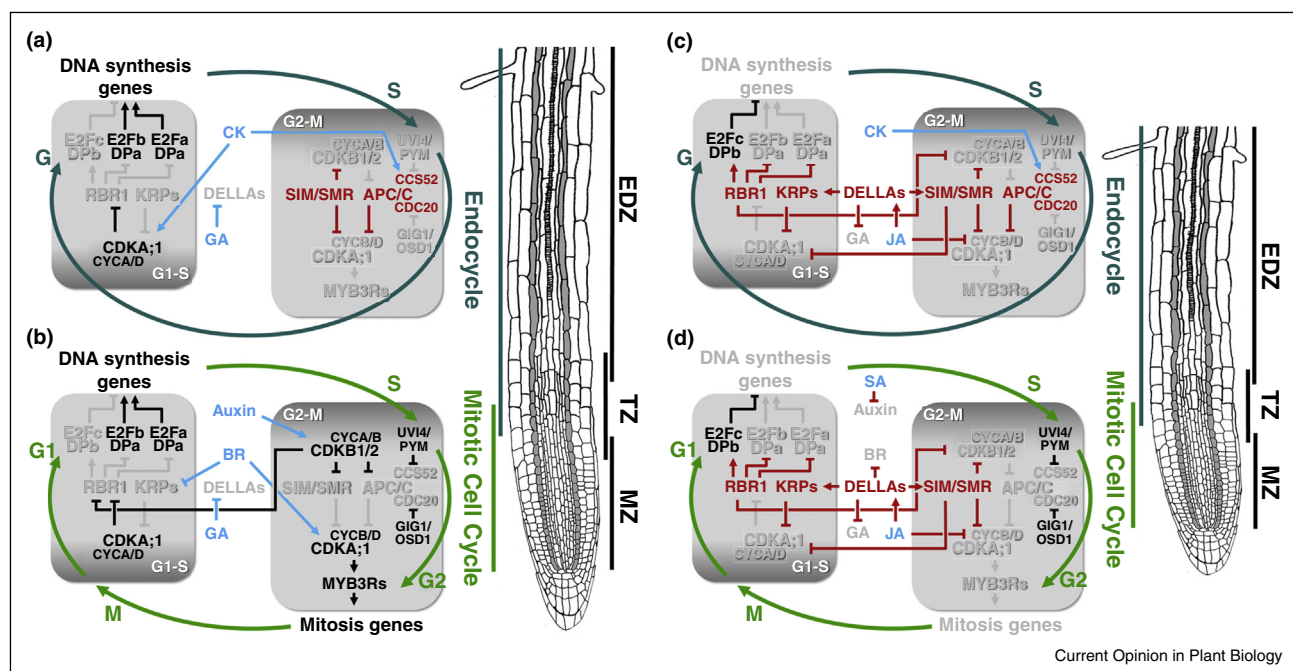
While these studies have advanced our understanding of the growth and immunity-related hormone interactions, it is still mostly unclear how this redirection of hormone activities translates into cellular processes regulating plant growth.

Hormones regulate the cell cycle

Growth depends on cell proliferation and expansion, which is regulated by the cell cycle machinery. The mitotic cell cycle (MCC) controls cell number at the root

stem cell niche and meristematic zone, whereas the endocycle enhances cell ploidy levels associated with cell expansion at the elongation zone [49,50]. The MCC is defined by four phases: Gap 1 phase (G1), followed by DNA synthesis (S) and Gap 2 phase (G2) and terminating in cell cycle exit after mitosis (M) (Figure 1a). Cell cycle progression depends on coordinated G1-S and G2-M transitions with CYCLIN-DEPENDENT-KINASES (CDKs) in complex with CYCLINS (CYCs) as the main regulators in these transitions. MCC entry is associated with the activation of CDKA;1 in complex with CYCD and CYCA3 as well as the CDKB1-CYCB/CYCA2 complex to phosphorylate the repressor RETINOBLASTOMA-RELATED1 (RBR1) [51,52**]. This essential step in G1-S transition allows heterodimerisation of the transcription factors E2Fa and E2Fb with DIMERISATION PARTNERa (DPa) to induce genes mediating DNA synthesis [53,54]. At the same time, SCF^{SKP2a} might degrade the repressor dimer E2Fc-DPb [55]. For the subsequent G2-M transition, CDKA;1-CYCD3/CYCB1 and CDKB1-CYCA3/CYCB complexes activate transcription factors (e.g. MYB3R) to induce genes participating in mitosis and cytokinesis [56].

Figure 1



Regulation of the cell cycle under non-stress and immunity. **(a)** Under non-stress conditions, the endocycle is active in the transition zone (TZ) and the elongation/differentiation zone (EDZ). During the endocycle, G1-S transition is mediated by the activation of the CYC-CDKA;1-E2F/DPa pathway, while the G2-M transition is inhibited by SIM/SMR and APC/C complex activity that is supported by CK. **(b)** In the meristematic zone (MZ) and partly in the TZ, cell division takes place. Here, CYC-CDKA;1 and CDKB-CYC complexes mediate G2-M transition, which is supported by auxin and brassinosteroids (BR). **(c)** Upon immune activation, G1-S transition can be blocked by DELLA activities on SIM/SMR and KRPs that might be supported by jasmonate (JA) signalling. JA further inhibits CYC-CDKA;1 complex activity and, hence, substantiates inhibition of G2-M transition. Further inhibition of the CYC-CDKA;1 activates RBR1 that, in turn, blocks CYC-CDKB complex activities. **(d)** Cell division is inhibited under immunity. In addition to the blockage of the CYC-CDKA;1-E2F/DPa pathway by KRPs, CYC-CDKA;1 and CYC-CDKB complexes are inactivated by JA, CK, DELLA and SA. As a result, cell proliferation and expansion is impaired resulting in stunted root growth. Grey and black colour indicates inactive and active pathways/proteins, respectively.

In contrast to the MCC, the endocycle does not enter mitosis and consists of a G and S phase resulting in repeated DNA synthesis cycles without cell division (Figure 1b). The establishment of the endocycle depends on KIP-RELATED PROTEINs (KRPs) and SIAMESE (SIM)/SIM-RELATED (SMR) to inhibit CDKA/B complex formation and, hence, G2-M transition [57,58]. Additionally, the E3 ligase ANAPHASE-PROMOTING COMPLEX/CYCLOSOME (APC/C) interacts with co-activators CELL CYCLE SWITCH 52 (CCS52) and CELL DIVISION CYCLE 20 [CDC20] to degrade CYCBs and CYCA2s and establish the endocycle [59,60]. Endocycle onset is antagonised by the interaction of UV-SENSITIVE4 (UVI4)/POLYCOMB (PVM) and GIGAS CELL1 (GIG1)/OMISSION OF SECOND DIVISION1 (OSD1) with CCS52A and CDC20 [61,62].

Auxin, BR, CK and GA play central roles in cell cycle regulation (Figure 1a,b). Auxin, BR and GA promote the initiation and progression of cell division. The reduced meristem sizes observed when BR and GA activities are disturbed, correlate with reduced *CYCB1;1* expression and, for BR only, enhanced *KRP2* expression [63^{••},64^{••}] as well as DELLA-mediated stabilisation of *KRP2* and induction of *KRP2*, *SIM* and *SMR*s [65]. Auxin induces *CYCA2;3* and *CYCB1;1* and elevates *CDKB2* gene and protein levels to promote MCC [66,67]. As auxin levels decrease towards the transition zone, CK levels increase to abort cell division and initiate endocycle entry and, hence, cell differentiation. Takahashi *et al.* [68b] identified CK-responsive ARABIDOPSIS RESPONSE REGULATOR2 (ARR2) binding to CCS52A to mediate endocycle entry. To summarise, any disturbance or redirection in hormone signalling can have significant impact on root growth and development and might explain immunity-triggered inhibition of root growth.

The redirection of the cell cycle machinery by immunity

Although our knowledge is still fragmentary it is obvious that immunity can significantly affect hormone-cell cycle networks (Figure 1c,d). For instance, SA-mediated inhibition of growth might be directly associated with its suppressive activity on auxin signalling [44]. In leaves, JA arrests growth by inhibiting MCC and endocycle [68a]. Interestingly, the reduced root meristem activity after JA treatment was found to be based on the suppression of genes participating in mitosis (e.g. *CDKA;1*, *CYCB1;1*), and this effect might be directly connected to DELLA stabilisation [48^{••},69^{••}]. Furthermore, the JA-regulatory TF MYC2 binds to the PLETHORA1 (PLT1) and *PLT2* promoters to suppress their transcription [69^{••}]. In concert with auxin, PLTs determine root growth and development by regulating cell division, stem cell maintenance and the root zonation (in the meristem, elongation, differentiation zone) [70]. The reduced meristem size and disturbed zonation pattern upon JA treatment might be

partially explained by antagonising auxin and PLT1/2 activities.

As immune responses involve hormones, such as JA, SA, GA and auxin, roots translate biotic stress into altered growth and development. Several studies identified a direct connection between immunity and the cell cycle machinery: In Arabidopsis, overexpression of *UVI4* and *OSD1* or loss of the atypical *DP-E2F-LIKE1* (*DEL1/E2Fe*) resulted in dwarfed phenotypes and enhanced resistance against *P. syringae* DC3000 and the powdery mildew fungus *Golovinomyces orontii*, respectively [71]. Interestingly, in addition to being a negative regulator of CCS52a2, *DEL1* was found to negatively regulate the SA transporter ENHANCED DISEASE SUSCEPTIBILITY5 (EDS5) [72^{••}]. The enhanced SA accumulation and slight dwarfism in *del1-1* was eliminated by deleting the SA synthase gene *ISOCHORISMATE SYNTHASE1* (*ICS1*). Consistent with this, silencing of SA signalling gene *PHYTOALEXIN-DEFICIENT 4* (*PAD4*) abolished stunted growth in *UVI4* and *OSD1* over-expressors [73^{••}]. Further, Bao *et al.* [73^{••}] revealed that enhanced resistance in *OSD1*-over-expressing lines was dependent on *CYCB1;1* and the R protein SUPPRESSOR OF NPR1-1, CONSTITUTIVE 1 (SNC1), providing a link between cell cycle regulation and ETI. The connection of ETI and the cell cycle was further substantiated by Wang *et al.* [74^{••}]. By searching for suppressors of the constitutive immunity mutant *cpr5*, Wang *et al.* identified *SIM* and *SMR1* both of these genes are required for ETI, dwarfism and elevated SA in *cpr5*. Based on their studies, CPR5 interacts with and negatively regulates *SIM* and *SMR1* at the nuclear membrane. Upon onset of ETI through pathogen effector recognition by NLRs, *SIM* and *SMR1* are released to support RBR1 hyperphosphorylation and subsequent over-activation of E2Fs to induce ETI-related cell death and immunity [74^{••}]. *SIM*/*SMR1*-dependent RBR1 hyperphosphorylation and E2Fs over-expression was unexpected because the cell cycle default functions of *SIM* and *SMR1* are to inhibit CDKs in order to prevent RBR1 phosphorylation and E2F activation. Moreover, the higher disease susceptibility of *sim smr* double mutants indicated the significance of their non-canonical activity in ETI. It will be important to decipher those mechanisms regulating the pleiotropic function of these proteins in cell cycle and ETI. From these studies it may be deduced that any biotic stress could redirect cell cycle function from growth into immunity, and that hormones (e.g. SA) are centrally involved in this switch.

Conclusions

A hyperactive immune system can be deleterious to plants and impair breeding efforts to enhance stress resistance in crops. This is most obvious from autoimmunity mutants and genetically incompatible combinations of allelic variants of positive PTI regulators (e.g. ACCELERATED CELL DEATH 6) resulting in highly resistant

but stunted plants [9,12,26**]. The studies reviewed here indicate that hormones take a central role in the underlying conflict between growth and immune signalling. In a multicellular plant, hormone-based communication elevates the efficiency and plasticity of organs such as roots by allocating tasks to cell types with different functional properties. This partitioning of functions requires a tight coordination between the different cell types. Under non-stress conditions, hormones coordinate cell proliferation, elongation and differentiation to support growth. Biotic stress redirects hormone activities towards immunity. What appears to be an inseparable hormone-regulated immunity or growth fate, can be unlinked. For example, chitin triggers immunity without affecting growth. Moreover, we recently identified the ability of a root colonising endophyte to separate immune and growth signalling upon flg treatment [75]. In order to understand the molecular basis of growth under immunity, we need to disassemble underlying hormone signalling networks. Root cell type-specific studies have advanced our knowledge of root development and revealed the cell type-specific regulation of meristem size and zonation pattern by hormones [63**,76,77]. Cell cycle regulators further showed a cell type-specific distribution, which might explain the expansion of CYCs in plants [78]. Therefore, efforts to genetically decipher the growth-immunity crosstalk require analyses at cell type resolution. Such studies will provide information of the spatio-temporal context of immune and growth pathways and their regulation through hormones. The recent re-evaluation of PLT and auxin functions in root development as well as the function of ABA and JA in integrating salt stress are indicative of cell type-specific hormone activities in regulating complex root responses [70,79].

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